| FORM PTO-1390 (REV. 11-2000) U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE | | ATTORNEY'S DOCKET NUMBER 512100-2025 |
|---|---|---|
| **TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371** | | U.S. APPLICATION NO. (If known see 37 C.F.R. 1.5) 10/031529 |
| INTERNATIONAL APPLICATION NO. PCT/EP00/06215 | INTERNATIONAL FILING DATE 04 JULY 2000 | PRIORITY DATE CLAIMED 22 JULY 1999 |

TITLE OF INVENTION **PHARMACEUTICAL COMPOSITION**

APPLICANT(S) FOR DO/EO/US **Achim BERTHOLD, Walter MÜLLER, Giovanni GAVIRAGHI**

Applicants herewith submit to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to promptly begin national examination procedures (35 U.S.C. 371(f)).
4. ☒ The US has been elected by the expiration of 19 months from the priority date (PCT Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☒ is attached hereto (required only if not communicated by the International Bureau).
   b. ☐ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ A English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

**Items 11 to 20 below concern document(s) or information included:**

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☐ A FIRST preliminary amendment.
14. ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 – 1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. ☒ Other items or information:

    PCT/RO/101, PCT/ISA/210, PCT/IB/308,
    PCT/IPEA/416, 409 (containing replacement pages 1, 1a, 9, 10, 10a for insertion into the International Application)
    2 Sheets of drawings

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| U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5) | INTERNATIONAL APPLICATION NO. | ATTORNEY'S DOCKET NO. |
|---|---|---|
| 10/031529 | PCT/EP00/06215 | 512100-2025 |

| 21. ☒ The following fees are submitted | CALCULATIONS PTO USE ONLY | |
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| **BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5):** Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37CFR 1.445(a)(2) paid to USPTO and International Search Report not prepared by the EPO or JPO ..... $1040.00 | | |
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| CLAIMS | NUMBER FILED | NUMBER EXTRA | RATE | | |
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| Total Claims | 12 - 20 = | 0 | x $18.00 | $ 0.00 | |
| Independent Claims | 1 - 3 = | 0 | x $84.00 | $ 0.00 | |
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**NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.**

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Dated: January 17, 2002

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28,029
REGISTRATION NUMBER

# Pharmaceutical composition

## Description

The present invention relates to a transdermal therapeutic system for the therapeutic administration of calcium antagonists of the dihydropyridine type, to a process for its preparation and to its use in medicine.

Calcium antagonists of the dihydropyridine type are compounds which influence the inflow of calcium ions into cells in particular into the cells of smooth muscles. Such compounds of the dihydropyridine type have been described, for example, in U.S. patent 3,799,934, U.S. patent 3,644,627, U.S. patent 4,264,611, and U.S. patent 4,801,599, which patents are incorporated by reference.

Calcium antagonists of the dihydropyridine type include, for example (without in any way limiting the scope of the invention), amlodipine, felodipine, isradipine, lacidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, and nitrendipine.

Diethyl (E)-4-[2-[(tert-butylcarbonyl)vinyl]phenyl-1,4-dihydro-2,6-dimethylpyridine-3,5 dicarboxylate (Lacidipine) is one of the preferred compounds of the dihydropyridine type. Lacidipine, which is described in British patent No. 2164336, is a potent long acting calcium antagonist which is particularly useful for treating hypertension. The compound may also be useful for the treatment of other cardiovascular disorders including atherosclerosis, peripheral vascular disease, ischaemic heart disease and congestive heart failure.

Nifedipine, which is described in U.S. patent 3,644,627, is another preferred calcium antagonists of the dihydropyridine type.

U.S. patent 4,983,395 pertains to transdermal drug delivery devices wherein the reservoir may comprise a gel consisting of nicardipine-hydrochloride, ® Klucel HF and a mixture of ethanol, water, glycerol and glycerol monooleate.

Transdermal drug delivery devices for co-administration of a drug such as nifedipine and a dual permeation enhancer comprising sucrose cocoate and methyl laurate are known from U.S. patent 4,956,171. The reservoir can contain nifedipine in methyl laurate or an aqueous solution of sucrose cocoate or in combination thereof.

EP-A 680,759 pertains to transdermal formulations of DHP calcium antagonists in a mixed liquid comprising cis-oleic acid and dimethylisosorbide dispersed in a propylene glycol base.

The promoting effect of a combination of limonene and ethanol has been found in Shirakura et al., Drug Development and Industrial Pharmacy, Vol. 21, No.4, 1995, pages 411 – 425 to synergistically enhance the transdermal adsorption of the DHP calcium antagonist NB-818.

Transdermal drug delivery systems provide a means for obtaining a high degree of control of drug concentration in the blood over a specified time period. Many systems have been developed and used to deliver drugs transdermally. It is however widely recognised that in general it is not possible to predict which particular systems will

provide a satisfactory delivery system with a specific drug substance if that has not previously been adminstered by that route.

We have now found that calcium antagonists of the dihydropyridine type may be advantageously administered transdermally from a drug reservoir containing a solution comprising a calcium antagonist of the dihydropyridine type and at least one skin permeation enhancer.

Thus in one aspect the present invention provides a transdermal therapeutic system (hereinafter TTS) for administering calcium antagonists of the dihydropyridine type which comprises (a) a backing layer, which defines the upper surface of the device (b) a drug reservoir containing a solution comprising a calcium antagonist of the dihydropyridine type and at least one skin permeation enhancer, (c) a membrane to control the release of the active ingredient, (d) a pressure sensitive adhesive layer for attaching the system to the skin and, if necessary, a release liner on the outer face of the adhesive layer wherein the said backing layer and said membrane are connected together to form the drug reservoir.

In a further aspect the present invention provides for the use of calcium antagonists of the dihydropyridine type for the manufacture of a TTS for administration of calcium antagonists of the dihydropyridine type through a pre-determined area of intact skin for the treatment of cardiovascular disorders including hypertension.

In a preferred embodiment, the present invention provides a TTS for administering calcium antagonists of the dihydropyridine type, especially lacidipine or nifedipine, in the form of skin patch.

Figure 1 of the accompanying drawings gives a schematic section of a transdermal therapeutic system according to the invention.

Figure 2 of the accompanying drawings gives a top view of a transdermal therapeutic system according to the invention prior to fill and sealing.

For a therapeutic transdermal system according to the invention the backing layer (1) is preferably made of a sheet or a film of a flexible material that is substantially impermeable to the solution of the calcium antagonist of the dihydropyridine type. The layer is preferably of the order of 50 – 200 μm in thickness and may be optionally pigmented. Conveniently the backing layer (1) is heat sealable to the control membrane (3).

The layer (I) is preferably of a material that permits the device to follow the contours of the skin and be worn comfortably on areas of the skin such as joints of flexure. Examples of flexible polymers useful for the backing layer include polyethylene, polypropylene, polyesters and the like, which may be provided as films or laminates. A preferred flexible polymer is a laminate consisting of pigmented polyethylene aluminium vapour coated polyester and a medium density polyethylene or ethylene vinyl acetate heat seal layer available from 3M™ under the trade mark Scotchpack ™1006.

The solution comprising a calcium antagonist of the dihydropyridine type and at least one skin permeation enhancer may be in a liquid, semisolid or thixotropic form and is contained within the drug reservoir (2).

A suitable amount of a calcium antagonist of the dihydropyridine type present in the solution is within the range 1 – 20 % e.g. 1 - 10 % by weight of the total solution.

Examples of suitable solvents for preparing the solution of a calcium antagonist of the dihydropyridine type include an alkanol e.g. ethanol, propanol or isopropanol or N-methyl-2-pyrrolidinone or mixtures thereof e.g. ethanol and N-methyl-2-pyrrolidinone.

Example of suitable skin permeation enhancers of this invention include saturated and unsaturated fatty acid esters, alcohols such as ethanol, propanol, isopropanol, n-decyl alcohol, etc, pyrrolidone derivatives (i.e. N-methyl-2- pyrrolidone) or (+)1-methyl-4-(1-methylethenyl)cyclohexene: ((+) limonene).

Conveniently fatty acid ester enhancers include esters of carboxylic acids containing from $C_8$ to $C_{16}$ carbon atoms. Preferred are those esters derived from palmitic acid, steric acid or lauric acid.

Conveniently fatty acid esters for use in the invention include fatty acid esters polyhydroxy alcohols such as sorbitol, glycerol or propylenglycol. Particularly preferred are fatty acids esters include those derived from sorbitol and of those sorbitan palmitate (Span™40) is particularly preferred.

Use of combinations of two or more of the skin permeation enhancer compounds may frequently result in superior results, such as greater transdermal absorption. Thus it has been found that a mixture of ethanol, N-methyl-2-pyrrolidone and sorbitan palmitate (Span™ 40) is a preferred skin permeation enhancing mixture.

The amount of ethanol present is conveniently within the range 10 - 60 % e.g. 30 - 40 % by weight of the total reservoir solution. The amount of Span™ 40 is conveniently within the range 0.5 - 6.0 % e.g. 1 - 5 % of the total reservoir solution. The amount of N-methyl-2-pyrrolidone present is conveniently within the range 20 - 70 % e.g. 40 - 70 % by weight of the total reservoir solution.

A particularly preferred reservoir solution of the invention contains 3 - 5 % e.g. 4 % of a calcium antagonist of the dihydropyridine type, such as lacidipine, 30 - 40 % e.g. 36.5 % of ethanol, 3 to 5 % e.g. 3.5 % of Span™ 40, and 50 - 60 % e.g. 56 % of N-methyl-2-pyrrolidone by weight of the total solution.

The solution comprising a calcium antagonist of the dihydropyridine type with one or more skin permeation enhancers forms a further aspect of the invention. This solution may be prepared by dissolving the calcium antagonist of the dihydropyridine type in a solution of the enhancers and the solvents using conventional procedures.

The membrane (3) to control the release of the calcium antagonist of the dihydropyridine type is a thin, flexible uniformly microporous, flat sheet membrane which provides a constant rate of drug release independent of time or of the amount of the active ingredient that remains in the reservoir. A preferred membrane is a flat sheet membrane made from food grade polypropylene and polyethylene resins

known under the Trade Mark Celgard™ 2400 or Celgard™ 2500, available from Hoechst Celanese. Celgard™ 2400 is the preferred membrane. Other suitable membranes include a microporus polyethylene membrane Solupor™ or an EVA membrane e.g. Co Tran™.

The contact adhesive layer (4) is a pressure-sensitive adhesive suitable for long term skin contact. It must also be physically and chemically compatible with the calcium antagonist of the dihydropyridine type and the vehicles employed. Further active ingredients must be soluble in the adhesive, so that the drug does not partition into the backing layer, but will partition into the skin. Conveniently the contact adhesive layer also adheres to the membrane (3).

Suitable adhesives include silicones, polyisobutylenes, polyacrilates, polyuretanes, plasticized ethylene, vinylacetate co-polymers, polystyrene-isoprene copolymer and a mixture thereof. Presently preferred contact adhesives are polyacrylates, silicones and polyurethanes.

Particularly preferred are the amine resistant silicone based pressure sensitive adhesives such as BIO-PSA Q7-4301, available from the Dow Corning Corp.

The release liner (5) is a disposable element which serves only to protect the adhesive layer prior to application to the skin. Typically, the release liner is formed from a material impermeable to the drug, vehicle, and adhesives and which is easily stripped from the contact adhesive.

Release liners are typically treated with silicone or fluorocarbons. A fluoro coated polyester film under the Trade Mark Scotchpatch™ 1022 available from 3M is particularly preferred.

In a further aspect of the invention provides a method for administering a calcium antagonist of the dihydropyridine type to a pre-determined area of intact skin, over defined time period and at an administration rate to reach and maintain an effective therapeutic dose of the calcium antagonist of the dihydropyridine type for the control

of hypertension and other cardiovascular diseases. In order to reach the effective blood levels of the drug a preferred rate of administration is between 0.1 to 2 μg/hr, more preferably in the range of 0.4 to 0.6 μg/hr, through a skin area of 2.0 to 90 $cm^2$, more preferably 10 to 40 $cm^2$. The amount of the drug delivered into the skin may be controlled by a number of factors, including skin patch size, degree of initial drug loading, the choice of skin permeation enhancers and the control release membrane.

The efficacy of the transdermal therapeutic system to deliver the calcium antagonist of the dihydropyridine type at the required rate and over the required time scale can be determined using conventional in vitro and in vivo test procedures. Thus for example using the in vitro procedure that is described by Franz J. T. Journal of Investigative Dermatology 64(3) 190 - 5 1975.

The present invention also provides a process for the production of the transdermal therapeutic system according to the invention which comprises the following steps:
a) coating the release liner (5) with the adhesive layer (4) which is then laminated with the control membrane (3);
b) securing the backing layer (1) to the control membrane (3) by means of a seal (7) so as to obtain the sachet (8) having an opening (6);
c) filling the reservoir (2) in the sachet (8) via the opening (6) with a solution comprising a calcium antagonist of the dihydropyridine type and at least one skin permeation enhancer and then sealing the opening (6);

In the preparation of the open reservoir sachet (8) it is convenient to use the backing layer (1) and the laminate comprising members (3), (4) and (5) in sheet form and when the said backing layer is sealed to the said laminate then the sachet (8) of the desired size and shape can be stamped or punched out either simultaneously with its formation or in a subsequent operation.

The individual TTS can be sealed into an appropriate packaging material using standard methods in the art. A convenient packaging material for use comprises a laminate of paper, polymer (i.e. polyethylene) and aluminium film. An example of a suitable means to seal the individual TTS into the appropriate packaging material is a polyethylene polymer available from Du Pont and known under Trade Mark Surlyn™

The example presented below serves to illustrate the invention without in any way limiting its scope:

Example 1

a) Preparation of the reservoir solution containing lacidipine – Dose per patch

N-methyl pyrrolidone(1.12 g) and sorbitan palmitate (Span™ 40) (0.07 g) were added to ethanol (0.737 g) and the solution obtained was stirred for about 30 min. Lacidipine (80 mg) was then added under stirring to obtain a homogeneous solution.

b) Preparation of the Transdermal Therapeutic System (TTS)

A solution of the silicone adhesive (4) [BIO-PSA Q7-4301: silicone resin, amine resistant, high tack 200 g/cm$^2$] was coated onto the release liner (5) [Scotchpak® 1022] . The control membrane (3) (Celgard® 2400) was then laminated to the dried adhesive layer. The backing layer (1) (Scotchpak® 1006) was then secured to the control membrane with a heat seal (7) to form a sachet (8) having a drug reservoir (2) connected to an opening (6). The drug reservoir (2) is then filled with the solution comprising lacidipine and at least one skin permeation enhancer via the opening (6) which is then heat sealed.

The patches of the following examples were prepared in an analogous manner

Example 2

Preparation of the reservoir solution containing nifedipine– Dose per patch

(+)-Limonene (0.37 g) was added to ethanol (1.60 g) and the solution obtained was stirred. Nifedipine (36 mg) was then added under stirring to obtain a homogeneous solution.

Example 3

Preparation of the reservoir solution containing nifedipine– Dose per patch

N-methyl pyrrolidone(1.12 g) and sorbitan palmitate (Span™ 40) (0.07 g) were added to ethanol (0.737 g) and the solution obtained was stirred for about 30 min. Nifedipine (82 mg) was then added under stirring to obtain a homogeneous solution.

New Claims

1. A transdermal therapeutic system for administering a calcium antagonist of the dihydropyridine type which comprises
   (a) a backing layer, which defines the upper surface of the device,
   (b) a drug reservoir containing a solution comprising
      - a calcium antagonist of the dihydropyridine type,
      - an alcohol selected from the group consisting of ethanol, propanol, isopropanol and n-decyl alcohol,
      - a pyrrolidone derivative, and
      - a saturated or unsaturated fatty acid ester of a carboxylic acid containing 8 – 16 carbon atoms and a polyhydroxy alcohol,
   (c) a membrane to control the release of the active ingredient, and
   (d) a pressure sensitive adhesive layer for attaching the system to the skin and, if necessary, a release liner on the outer face of the adhesive layer wherein the said backing layer and said membrane are connected together to form the drug reservoir.

2. A transdermal therapeutic system as claimed in claim 1 wherein the solution in the drug reservoir comprises a calcium antagonist of the dihydropyridine type, ethanol, N-methyl-2-pyrrolidinone and sorbitan palminate.

3. A transdermal therapeutic system as claimed in claim 2 wherein the solution comprises a calcium antagonist of the dihydropyridine type 3 - 5 %, ethanol 30 - 40 %, sorbitan palmitate 3 - 5 % and N-methyl-2-pyrrolidinone 50 - 60 % by weight of the total solution.

4. A transdermal therapeutic system as claimed in any of claims 1 to 3 in the form of skin patch.

5. A transdermal therapeutic system as claimed in any of claims 1 to 4 in which the calcium antagonist of the dihydropyridine type is selected from the group consisting of amlodipine, felodipine, isradipine, lacidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, and nitrendipine.

6. A transdermal therapeutic system as claimed in any of claims 1 to 5 in which the calcium antagonist of the dihydropyridine type is lacidipine.

7. A transdermal therapeutic system as claimed in any of claims 1 to 5 in which the calcium antagonist of the dihydropyridine type is nifedipine.

8. The use of a calcium antagonist of the dihydropyridine type for the manufacture of a transdermal therapeutic system as claimed in any of claims 1 to 7 for administration of a calcium antagonist of the dihydropyridine type through a pre-determined area of intact skin for the treatment of cardiovascular disorders including hypertension.

9. A method for administering a calcium antagonist of the dihydropyridine type through a pre-determined area of intact skin and at an administration rate such as to reach and maintain an effective therapeutic dose of a calcium antagonist of the dihydropyridine type for the control of hypertension and other cardiovascular diseases which comprises applying to the skin a transdermal therapeutic system as claimed in any of claims 1 to 7.

10. A solution which is suitable for use in a transdermal therapeutic system as claimed in any of claims 1 to 7 which comprises
a drug reservoir containing a solution comprising
- a calcium antagonist of the dihydropyridine type,
- an alcohol selected from the group consisting of ethanol, propanol, isopropanol and n-decyl alcohol,
- a pyrrolidone derivative, and
- a saturated or unsaturated fatty acid ester of a carboxylic acid containing 8 – 16 carbon atoms and a polyhydroxy alcohol.

11. A solution as claimed in claim 10 which comprises a calcium antagonist of the dihydropyridine type, ethanol, N-methyl-2-pyrrolidinone and sorbitan palmitate.

12. A method of treating hypertension which comprises administering an effective amount of a calcium antagonist of the dihydropyridine type in a transdermal therapeutic system as claimed in any of claims 1 to 7.

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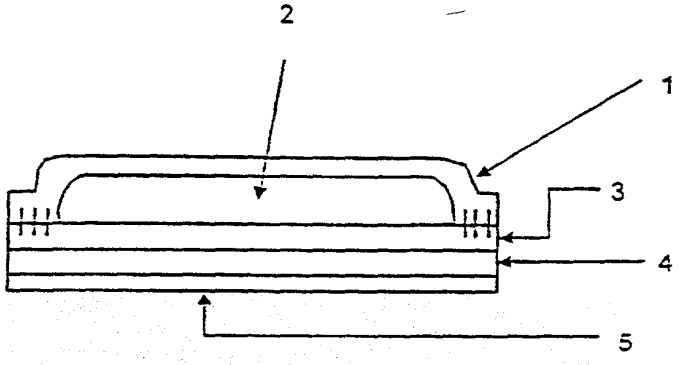
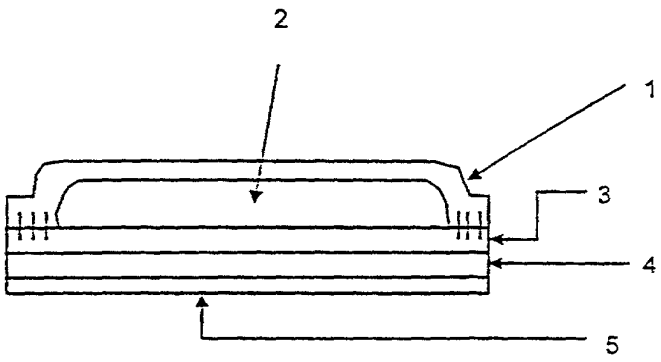
schematic section of a TTS according to the invention



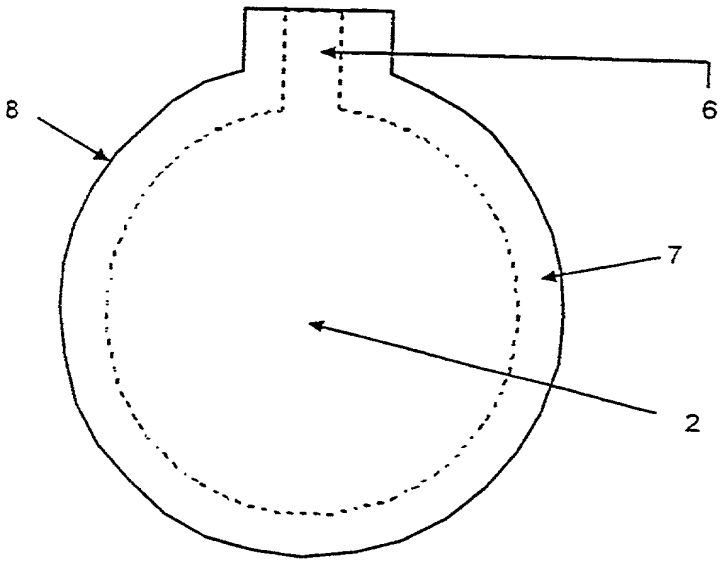

(57) Abstract: The invention relates to transdermal therapeutic systems for the therapeutic administration of calcium antagonists of the dihydropyridine type, to a process for its preparation and to its use in medicine.

WO 01/07017 A1

Fig. 1: schematic section of a TTS according to the invention



Fig, 2: top view of TTS according to the invention prior to filling and sealing



**COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY**

As below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below, I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

**Pharmaceutical composition**

the specification of which
- is attached hereto
- was filed on

and including all the amendments through the date hereof.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, § 119 of any foreign application (s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

**Prior Foreign Application (s) for which Priority is Claimed**:

1.) Great Britain, 9917290.0 of July 22, 1999

And I hereby appoint
William F. Lawrence, Registration ~~No. 28,029~~, of the firm FROMMER LAWRENCE & HAUG, LLP whose post office address is 745 Fifth Avenue, New York, New York 10151, or their duly appointed associate, my attorneys, with full power of substitution and revocation, to prosecute this application, to make alterations and amendments therein, to file continuation and divisional application thereof, to receive the Patent, and to transact all business in the Patent and Trademark Office and in the Courts in connection therewith, and specify that all communications about the application are to be directed to the following correspondence address:

William F. Lawrence, Esq.
c/o FROMMER, LAWRENCE & HAUG LLP
745 Fifth Avenue
New York, New York 10151

Direct all telephone calls to:
(212) 588-0800, to the attention
of : William F. Lawrence

**COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY**

As below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below, I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

**Pharmaceutical composition**

the specification of which
- is attached hereto
- was filed on

and including all the amendments through the date hereof.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

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1999/121 US

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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2) ~~Dr. Walter Müller, Engerserstrasse 56, 56564 Neuwied, Germany~~
3) ~~Dr.~~ Giovanni Gaviraghi, Glaxo Welcome S.p.A., Via A. Fleming 2, 37~~100~~ Verona, Italy ITX

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Signature: _____ Date: _____

Signature: _____ Date: _____

Signature: Giovanni Gaviraghi Date: 7 Dec 7th 2001

The inventors 1.) and 2.) are citizens of Germany.
The inventor 3.) is citizen of Italy.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Signature: Achim Berthold Date: Dec. 7th 2001

Signature: Walter Müller Date: Dec. 7th 2001

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